Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	9/26/2018
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

SHOX Deficiency Disorders, Sequencing and Deletion/Duplication

ARUP test code 3004603

SHOX Specimen: Whole Blood

SHOX Interp: Positive

RESULT
Two copies of a pathogenic variant were detected in the SHOX gene.

PATHOGENIC VARIANT
Gene: SHOX (NM_000451.3)
Nucleic Acid Change: Deletion of CNE-2 through exon 2 Homozygous
Inheritance: Pseudoautosomal dominant/recessive

INTERPRETATION
Two copies of a pathogenic variant, deletion of CNE-2 through exon 2, were detected in the SHOX gene by Multiplex Ligation-dependent Probe Amplification (MLPA) analysis. This molecular result is consistent with a diagnosis of Langer mesomelic dysplasia (LMD), which is associated with biallelic SHOX inactivation. All of this individual's future offspring will inherit one copy of the pathogenic deletion regardless of sex. Heterozygous pathogenic variants in SHOX are causative for SHOX-related haploinsufficiency disorders such as Leri-Weill dyschondrosteosis (LWD) or idiopathic/isolated short stature (ISS).

No additional pathogenic variant is detected by massively parallel sequencing. Please refer to the background information included in this report for the methodology and limitations of this test.

Evidence for variant classification:
The SHOX deletion of CNE-2 through exon 2 deletes upstream non-coding elements and the first part of the SHOX gene. Deletions of exons 1-2 and upstream CNE elements have been described in individuals affected with Leri-Weill dyschondrosteosis (LWD) (Benito-Sanz 2006, Benito-Sanz 2017, Bunyan 2013, Shima 2016). Based on available information, this deletion is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified pathogenic deletion (Deletion/Duplication Analysis by MLPA, ARUP test code 3003144). If clinically indicated, this individual's future reproductive partner should be offered SHOX testing (SHOX Deficiency Disorders, Sequencing and Deletion/Duplication, ARUP test code 3004603), as biallelic SHOX inactivation is associated with

H=High, L=Low, *=Abnormal, C=Critical

Langer mesomelic dysplasia (LMD).

COMMENTS
Likely benign and benign variants are not reported.

REFERENCES
Benito-Sanz S et al. Characterization of SHOX deletions in Leri-Weill dyschondrosteosis (LWD) reveals genetic heterogeneity and no recombination hotspots. Am J Hum Genet. 2006 Aug;79(2):409-14. PMID: 16826534.

Benito-Sanz S et al. Identification of 15 novel partial SHOX deletions and 13 partial duplications, and a review of the literature reveals intron 3 to be a hotspot region. J Hum Genet. 2017 Feb;62(2):229-234. PMID: 27604558.

Bunyan DJ et al. Diagnostic screening identifies a wide range of mutations involving the SHOX gene, including a common 47.5kb deletion 160kb downstream with a variable phenotypic effect. Am J Med Genet A. 2013 Jun;161A(6):1329-38. PMID: 23636926.

Shima H et al. Systematic molecular analyses of SHOX in Japanese patients with idiopathic short stature and Leri-Weill dyschondrosteosis. J Hum Genet. 2016 Jul;61(7):585-91. PMID: 26984564.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: SHOX Deficiency Disorders, Sequencing and Deletion/Duplication

CHARACTERISTICS: Pathogenic variants in the SHOX gene result in a spectrum of disorders due to haploinsufficiency of the SHOX gene. Clinical features often include short stature, mesomelia (shortening of the lower portion of arm and leg), and abnormal alignment of the radius, ulna, and carpal bones at the wrist (Madelung deformity). Variable expressivity results in some individuals only affected with isolated short stature (ISS), while others have short stature and additional findings resulting in syndrome disorders (e.g., Leri-Weill dyschondrosteosis [LWD] or Langer mesomelic dysplasia [LMD]).

EPIDEMIOLOGY: Prevalence of SHOX deficiency disorders is estimated to be at least 1 in 1,000 individuals.

CAUSE: A single pathogenic variant in the SHOX gene causes ISS or LWD. Biallelic pathogenic variants in the SHOX gene cause LMD.

INHERITANCE: SHOX is located in the pseudoautosomal region 1 (PAR1) on the X and Y chromosomes and escapes X-inactivation. Thus, inheritance is pseudoautosomal dominant for ISS and LWD, and pseudoautosomal recessive for LMD.

PENETRANCE: High, with variable expressivity

CLINICAL SENSITIVITY: At least 90 percent in individuals with SHOX deficiency disorders. Approximately 10 percent of individuals with LWD do not have a demonstrable SHOX pathogenic variant.

GENE TESTED: SHOX (NM_000451)
Exon 6b (NM_006883) is not covered by sequencing.

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and to confirm reported variants that do not meet acceptable quality metrics. Multiplex ligation-dependent probe amplification (MLPA) of the SHOX gene.

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions (indels) from 1-10 base pairs in size. Indels greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced. The analytical sensitivity for MLPA is greater than 99 percent.

LIMITATIONS: A negative result does not exclude a SHOX deficiency disorder. This test only detects variants within the coding regions and intron-exon boundaries of the SHOX gene. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants and deep intronic variants will not be identified. Precise breakpoints for large deletions or duplications are not determined in this assay and single exon deletions/duplications may not be detected based on the breakpoints of the rearrangement. The actual breakpoints for the deletion or duplication may extend beyond or be within the exon(s) reported. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations caused by the presence of pseudogenes, repetitive, or homologous regions. This test is not intended to detect low-level mosaic or somatic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) variants, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

SNVs and indels will not be called in the following regions due to technical limitations of the assay: SHOX (NM_006883) exon 6, also known as exon 6b.

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the U.S. Food and Drug Administration. This test was performed in a CLIA-certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
SHOX Specimen	23-044-115809	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
SHOX Interp	23-044-115809	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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